13. A method according to claim 4 wherein said cellular phenotype is cell cycle regulation and said cellular parameters comprise cell viability, proliferation, and cell phase.

14. A method according to claim 8 wherein said cells are tumor cells.--.

REMARKS

Claims 1-14 are now pending. The present claims are provided in an attached appendix for the Examiner's convenience.

The specification has been amended to comply with 37 C.F.R. § 1.78 by providing a specific reference to the earlier applications to which the present application claims the benefit of priority. Support is found in the Form 1.16b which accompanied the present application. The specification has also been amended to correct obvious typographical errors.

Claims 1 and 3 have been amended to specify that the cellular parameters allow detection of alterations in cellular phenotype and that alteration in cellular phenotype indicates that the candidate is a bioactive agent capable of altering a cellular phenotype. Support is found, for example, at page 8, lines 12-24.

Claims 5 and 7 have been amended so that they are no longer multiple dependent claims. Claims 11 and 13 have been added to replace Claims 5 and 7 in so far as they were dependent from Claim 4, while Claim 12 has been added to replace claim 6 in so far as it was dependent from claim 4. Support for these new claims is found in original Claims 5-7.

Claim 9 is amended to limit its dependence from Claims 1 or 2. Claim 14 is added to replace amended Claim 9 in so far as it was dependent from Claim 8. Support for this new claim is found in original Claim 9.

Objections

The applications to which the present application claims priority have been specifically referenced in the first sentence of the specification.

Formal drawings will be submitted upon the finding of allowable subject matter and the issuance of a Notice of Allowance.

A letter to the Draftsman is enclosed showing the proposed changes in red to indicate Figures 1A-1C.

The objection to the lack of Seq. ID. Nos. is addressed in the accompanying Preliminary Amendment submitted in response to the Notice to Comply.

The specific syntax errors referred to by the Examiner, as well as several others discovered by the Applicants, are addressed in the present amendments.

Claims 8-10 are objected to under 37 C.F.R. 1.75(c) as being multiple dependent claims depending from multiple dependent claims (page 11 of Office Action). These claims have been amended.

35 U.S.C. § 112 Rejections

Claims 1-7 are rejected under 35 U.S.C. § 112, first paragraph as being non-enabling. Applicants respectfully traverse.

The test for enablement under 35 U.S.C. § 112, first paragraph, is whether a claim is supported by the disclosure such that one of ordinary skill in the art could make and use the invention at the time the application was filed (*see* MPEP § 2164). Applicants submit that the present methods are enabled for use with a multitude of candidate bioactive agents and various cell types, as disclosed in the specification.

The Office Action suggests that the present methods are not enabled because the specification does not provide enablement "a library of bioactive agents and a population of cells" to be used in the present methods. Applicants respectfully point out that the claims currently in issue are directed toward methods of screening for a bioactive agent capable of altering a cellular phenotype. The present claims do not require a library of bioactive agents for use. Rather, the claims include the use of a candidate bioactive agent, or libraries of bioactive agents, and allow the identification of

whether the candidate agent is a bioactive agent. The skilled artisan would reasonably expect to perform the claimed methods without undue experimentation.

The specification provides extensive description of many compounds encompassed by the phrase "candidate bioactive agent" (*see* page 16, line 8 to page 30, line 34). However, the specification teaches that the candidate may be "any molecule". The specification makes clear that the candidate bioactive agent is not a limiting factor for the present methods because capability of the bioactive agent to alter a cellular phenotype need not be known prior to the use of the agent in the present methods. Rather, candidate bioactive agents are employed, and their bioactivity determined by the claimed methods. As the Examiner will appreciate, libraries of candidate agents are well known.

A feature of the claimed methods is the use of multiple cellular parameters (at least three or at least five) to screen for a bioactive agent capable of altering a cellular phenotype. The specification repeatedly teaches that using multiple cellular parameters to assay for alterations in cellular phenotype, as described therein, increases specificity and reduces background of such assays. The many assays that may be used in the claimed methods are extensively described in the specification (*e.g.*, page 8, lines 20-28, page 10, line 29 to page 16, line 6, page 31, line 23 to page 32, line 4, page 32 lines 22-27 and page 34, line 19 to page 41, line 27), and the specification provides a dozen working examples of such assays and teaches how they may be combined to provide the presently claimed methods. Moreover, these assays may be used in conjunction with a variety of cell types.

For the reasons discussed above, Claims 1-7 satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. Therefore, the Examiner is respectfully requested to withdraw this rejection.

Claim 1 is rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Applicants respectfully traverse.

The Office Action states that the claim "does not recite positive process steps of screening for said bioactive agents." Applicants again clarify that the claim is for a method of screening for a bioactive agent, not screening of already identified bioactive

agents. The amended claims provide the positive steps of: a) combining at least one candidate bioactive agent and a population of cells; and b) sorting said cells in a FACS machine by separating said cells on the basis of at least five cellular parameters which allow detection of alterations in cellular phenotype, whereby said alteration in cellular phenotype indicates said candidate is a bioactive agent capable of altering a cellular phenotype. By this method, bioactive agents capable of altering a cellular phenotype are identified.

For the reasons discussed above, Claim 1 satisfies the requirements of 35 U.S.C. § 112, second paragraph. Therefore, the Examiner is respectfully requested to withdraw this rejection.

The objection to Claims 8-10 under 37 C.F.R. § 1.75(c) is discussed above in the initial remarks. Specifically, the claims have been amended to remove improper dependency. Applicants therefore request that the objection be withdrawn.

Provisional Rejections

Claims 1-3 and 5-6 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 12-33 and 35 of copending Application No. 09/062,333. Claims 1-7 are provisionally rejected under the same doctrine as being unpatentable over claims 1-3 and 5 of copending Application No. 09/157,748.

Applicants request that the Examiner hold these rejections in abeyance until such time as otherwise patentable subject matter is found.

Claims 1-7 are provisionally rejected under 35 U.S.C. § 103(a) as being obvious over copending Application No. 09/157,748. Applicants respectfully traverse.

The Examiner states that this rejection may be overcome if any invention disclosed but not claimed in the copending application was derived from the inventor of this application. Applicants point out that the '748 application has only a single inventor who is also an inventor on the present application. Therefore, any invention disclosed in

the '748 application could not have been invented by one not named as an inventor in the present application.

For the reasons discussed above, applicants respectfully request that the Examiner withdraw this provisional 35 U.S.C. § 103(a) rejection.

35 U.S.C. § 102 Rejections

Claims 1-4 and 7 are rejected under 35 U.S.C. § 102(a) as being anticipated by Nolan (WO 97/27212). Applicants respectfully traverse.

For a reference to anticipate a claim, it must teach each and every element of the claim (*see* MPEP § 2131 and references cited therein). The present claims are not anticipated by the disclosure of Nolan because Nolan does not teach sorting cells in a FACS machine by separating cells on the basis of at least five (Claims 1-2) or at least three (Claims 3-4 and 7) cellular parameters. Nolan teaches the separation of cells based on a single reporter gene.

The Office Action cites several passages from the Nolan reference to support this rejection. The majority of these passages are not related to the sorting of cells in a FACS machine. Where sorting of cells by FACS is addressed, it refers to detection of the expression of reporter genes to measure infection, integration and expression of a virus (page 28, lines 25-29), the presence or level of a particular cell or molecule (page 31 line 7 to page 32, line 6), and measurement of the level of a reporter gene (Example 4). Nowhere does Nolan teach or suggest sorting cells in a FACS machine by separating the cells on the basis of at least three or five cellular parameters.

Claim 3 is rejected under 35 U.S.C. § 102(e) as being anticipated by Kamb (USPN 5,955,275). Applicants respectfully traverse.

Applicants reiterate that Claim 3 has the element of sorting cells in a FACS machine by separating cells on the basis of at least three cellular parameters. However, Kamb teaches the separation of cells based on a single reporter gene.

The Office Action cites several passages to support this rejection. It is apparent from reading each of the cited passages, however, that Kamb only contemplates the use of FACS to separate cells based on the expression of a single gene. In some instances, it is expression of an inserted fluorescent gene linked to a phenotype-

associated promoter (e.g., Example 2). In Example 3, the expressed cell surface gene is detected using a fluorescently labeled antibody. However, Kamb does not suggest separating cells on the basis of at least three cellular parameters. As with Nolan, at best, Kamb teaches sorting cells using FACS on the basis of a single parameter.

Based on the discussion above, Claims 1-4 and 7 are not anticipated by Nolan and Claim 3 is not anticipated by Kamb. Therefore, the Examiner is respectfully requested to withdraw these 35 U.S.C. § 102 rejections.

35 U.S.C. § 103 Rejection

Claims 5-6 are rejected under 35 U.S.C. § 103(a) as being obvious over either Nolan or Kamb in view of Hide et al., J. Cell Biol. 123(3):585-93 (1993). Applicants respectfully traverse.

As discussed above, neither Nolan nor Kamb teach or suggest all of the elements of Claim 3, from which Claims 5 and 6 depend. Hide et al. does not cure this shortcoming because this reference also does not disclose or suggest sorting cells in a FACS machine by separating cells on the basis of at least three cellular parameters. Nor would the combination of any or all of these references provide the presently claimed invention, even if one were motivated to combine them. And given the limited use of a single reporter as a means for detecting cellular phenotype found in Nolan and Kamb, one of ordinary skill in the art would not reasonably expect to be able to sort cells in a FACS machine by separating them on the basis of at least three cellular parameters.

To show obviousness, each element must be disclosed in the combination of references, there must be suggestion or motivation to combine the references, and there must be a reasonable expectation of arriving at the claimed subject matter by combining the references. Based on the above discussion, a *prima facie* case of obviousness has not been shown. Therefore, the Examiner is respectfully requested to withdraw the 35 U.S.C. § 103(a) rejection of Claims 5 and 6.

Applicants submit that the Claims are now in form for allowance and earnestly request such a finding. If after review of this response, the Examiner has further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

Respectfully submitted,

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APPENDIX

1. (Amended) A method of screening for a bioactive agent capable of altering a cellular phenotype, said method comprising:

a) combining at least one candidate bioactive agent and a population of cells; and

b) sorting said cells in a FACS machine by separating said cells on the basis of at least five cellular parameters which allow detection of alterations in cellular phenotype, whereby said alteration in cellular phenotype indicates said candidate is a bioactive agent capable of altering a cellular phenotype.

2. A method according to claim 1 wherein a library of candidate bioactive agents are combined with said population.

3. (Amended) A method of screening for a bioactive agent capable of altering a cellular phenotype, said method comprising:

a) introducing a library of nucleic acids each encoding a candidate bioactive agent into a population of cells; and

b) sorting said cells in a FACS machine by separating said cells on the basis of at least three cellular parameters which allow detection of alterations in cellular phenotype, whereby said alteration in cellular phenotype indicates said candidate is a bioactive agent capable of altering a cellular phenotype.

4. A method according to claim 3 wherein said library is a retroviral library.

5. (Amended) A method according to claim 3 [or 4] wherein said cellular phenotype is exocytosis and said cellular parameters are selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins.

6. A method according to claim 5 further comprising subjecting said cells to conditions that normally cause exocytosis.

7. (Amended) A method according to claim 3 [or 4] wherein said cellular phenotype is cell cycle regulation and said cellular parameters comprise cell viability, proliferation, and cell phase.

8. (Amended) A method according to claim 3, 4, 5, 6, [or] 7, 11, 12 or 13 wherein said nucleic acids comprise fusion nucleic acids comprising:

a) said nucleic acid encoding said candidate bioactive agents; and

b) a detectable moiety.

9. (Amended) A method according to claim [1, 2, 3, 4, 5, 6, 7 or 8] 1 or 2 wherein said cells are tumor cells.

10. A method according to claim 8 wherein said detectable moiety is a fluorescent protein.

--11. A method according to claim 4 wherein said cellular phenotype is exocytosis and said cellular parameters are selected from the group consisting of light scattering, fluorescent dye uptake, fluorescent dye release, annexin granule binding, surface granule enzyme activity, and the quantity of granule specific proteins.

12. A method according to claim 11 further comprising subjecting said cells to conditions that normally cause exocytosis.

13. A method according to claim 4 wherein said cellular phenotype is cell cycle regulation and said cellular parameters comprise cell viability, proliferation, and cell phase.

14. A method according to claim 8 wherein said cells are tumor cells.--